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(54) Domperidone and NSAIDs for the treatment of migraine

(57) Analgesic and anti-inflammatory compositions including domperidone in combination with a non-steroidal anti-inflammatory (NSAID), e.g. ibuprofen, and also a narcotic analgesic, e.g. codeine, are used to treat nausea and vomiting caused by migraine attacks. The compositions may be in the form of tablets, capsules, granules, liquids or suppositories.

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ANALGESIC AND ANTI-INFLAMMATORY COMPOSITIONS COMPRISING DOMPERIDONE AND METHODS OF USING SAME.

BACKGROUND TO THE ART

The current means of combating migraine attacks include simple analgesics such as aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDS) and paracetamol, taken at the earliest signs of an attack [1, 2, 3]. Aspirin, paracetamol and phenacetin have long been among the most commonly used members of the NSAIDS class. Amongst the newer NSAIDS are ibuprofen, ketoprofen, mefenamic acid, diflunisal, naproxen and piroxicam. The most widely used NSAIDS available over the counter that have fewer gastro intestinal side effects than aspirin are paracetamol and ibuprofen.

Combined preparations of paracetamol or aspirin with an anti-emetic agent such as buclizine or metoclopramide, have been used to alleviate the nausea symptoms that often accompanied a migraine attack. Commercially, they are available as Migraleve Duo®, Paramax®, Migravess®. Narcotic analgesics such as codeine have also been employed together with NSAIDS to obtain synergistic analgesia, for example Migraleve Yellow®, co-codamol.

Gastric stasis, commonly present in migraine[4], causes the poor absorption of the analgesics. Dispersible and effervescent formulations have been used in an attempt to overcome this[4]. Metoclopramide, an anti-emetic, also relieves gastric stasis which has been found useful counteracting the reduced analgesic effects of paracetamol in migraine attacks [1, 4, 5].

Attacks who do not respond to analgesics may be treated with ergot preparations such as ergotamine tartrate. Newer alternatives to ergot compounds for acute migraine are the selective serotonin $5HT_1$ agonist, for example Sumatriptan®[6, 7]. Recent trials reported that oral 100 mg sumatriptan to be as effective as aspirin 900 mg plus 10 mg metoclopramide for initial attacks and more effective in subsequent attacks [8].

The use of metoclopramide combined with either paracetamol, or aspirin has already been disclosed. Domperidone is a dopamine antagonist but is less likely than metoclopramide to produce extra pyramidal side effects since it does not cross the blood brain barrier. It stimulates gastro-intestinal mobility and is used in the management of nausea and vomiting. The activity of domperidone on the gastro intestinal mobility could enhance the rate of absorption of the

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analgesics. In Cephalagia 13 (2), 124-7 (1993), the safety and efficacy of separately administered domperidone in combination with paracetamol in the treatment of acute attack of migraine was demonstrated. The method of making a film coated tablet containing paracetamol and domperidone is disclosed in WO95/22974.

As far as the inventor knows, the art has never suggested that domperidone either be added to selected NSAIDS, which differ substantially in chemical structure from paracetamol; or be added to selected NSAIDS together with selected narcotic analgesic drugs. Also, the prior art does not suggest the use of any two-component composition of a selected NSAID and domperidone; and three-component of a selected NSAID, a selected narcotic analgesic and domperidone to hasten the analgesic response and to manage nausea symptoms in migraine attacks.

DETAILED DESCRIPTION OF THE INVENTION

The NSAIDS for use in the compositions and methods of the present invention can be selected from the following categories:

1) the propionic acid derivatives

2) the acetic acid derivatives;

3) the fenamic acid derivatives;

4) the biphenylcarboxylic acid derivatives;

5) the oxicams.

All the contemplated compounds can be used at appropriate dosage levels for the purpose in the composition of the present invention. The compounds in groups 1 to 4 typically contain a carboxylic acid function; however, those acids are sometimes administered in the form of their pharmaceutically acceptable salts, e.g. sodium salts.

The propionic acid derivatives for use herein include, but are not limited to, ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaprozin, prapoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen, and bucloxic acid. Structurally related propionic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Presently preferred members of the propionic acid group include ibuprofen, naproxen, flurbiprofen, fenoprofen, ketoprofen and fenbufen.

The acetic acid derivatives for use herein include, but not limited to, indomethacin, sulindac, tolmetin, zomepirac, diclofenac, fenchlofenac, alchlofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac and oxipinac. Structurally related acetic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Presently, preferred members of the acetic acid group include tolmetin sodium, zomepinac sodium, sulindac and indomethacin.

The fenamic acid derivatives for use herein include, but are not limited to, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid and tolfenamic acid. Structurally related fenamic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to encompassed by this group. Presently, preferred members of the fenamic acid group include mefenemic acid and meclofenamate sodium (meclofenamic acid, sodium salt).

The biphenylcarboxylic acid derivatives for use herein include, but are not limited to, diflunisal and flufenisal. Structurally related biphenylcarboxylic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Preferred members of this group are diflunisal and flufenisal.

The oxicams for use herein include, but are not limited to, piroxicam, sudoxicam, isoxicam. Structurally related oxicams having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. A preferred member of this group is piroxicam.

The narcotic analgesics for use in the present invention are orally active narcotic agonists. Suitable agonist-antagonist for use herein include orally analgesically active antagonists of the nalorphine type, notably pentazocine; and orally analgesically active antagonists of the morphine type, notably buprenorphine. Another suitable agonist-antagonist is meptazinol. Suitable narcotic agonists for use herein include orally analgesically active members of the morphine group, notably codeine, oxycodone, dihydrocodeine, dextropropoxyphene, papaveretum and tramadol. In many instances, the narcotic analgesics for use herein are administered in the forms of their pharmaceutically acceptable acid addition salts, e.g. codeine sulphate, codeine phosphate, dihydrocodeine tartrate and tramadol hydrochloride. Structurally related analogues to the aforementioned compounds having similar analgesic property are also intended to be encompassed by this group.

For compounds (NSAIDS or narcotic analgesics) which have optically active centre(s), the invention refers to the racemate as well as the pure (-) or (+) optical isomeric forms.

The domperidone or its analogues used herein is intended to encompass not only domperidone as the anhydrous powered but any salt or derivatives or any compounded mixture thereof which is non toxic, pharmaceutically acceptable and which has gastric motility stimulating activity to enhance absorption of the co-administered analgesic(s) in gastric stasis and anti-emetic property. Presently, the preferred salt of domperidone is maleate.

The term "selected NSAID" as used herein is intended to mean any non-narcotic analgesic/nonsteroidal anti-inflammatory compound within one of the five structural categories indicated hereinabove. Similarly, the term "selected narcotic analgesic" as used herein is intended to mean any orally analgesically active narcotic analgesic, be it an orally active narcotic agonist having oral analgesic activity. The terms "selected NSAID" and "selected narcotic analgesic" are used for the sake of simplicity in the discussion which follows.

When a selected NSAID or NSAID plus a selected narcotic analgesic is combined with domperidone in accord with the present invention, the following results may be produced:

- the analgesic/anti-inflammatory effect of the selected NSAID as a single active or NSAID plus a selected narcotic analgesic can be brought on more quickly;

- the nausea symptom experienced in acute migraine attacks can be averted or alleviated.

For pauents suffering migraine headache, the time from administration of medication to the onset of effective relief is clearly of paramount importance. The hastening of the onset analgesia by combining domperidone with a selected NSAID or a selected NSAID plus a selected narcotic

[redacted]

The precise amount of NSAID or narcotic analgesic drug for use in the present compositions will vary depending, for example, on the specific drug chosen, the condition for which the drug is administered. Generally speaking, the selected NSAID or narcotic analgesic can be employed in any amount known to be an effective analgesic and anti-inflammatory amount.

Typical effective analgesic amounts of presently preferred NSAIDs/narcotic analgesic for use in unit dose compositions of the invention can be found in the British National Formulary, American Hospital Formulary, Martindale Extra Pharmacopoeia, e.g. 50 - 600 mg Ibuprofen. In a two-component composition of a selected NSAID and domperidone and a three component composition of a selected NSAID, a selected narcotic analgesic and domperidone, the daily analgesic dose for each analgesic will generally not exceed their daily analgesic dosages. The ratio of a selected NSAID to a selected narcotic analgesic may vary depending on the particular drugs selected and the required analgesic response.

While the compositions of the invention are preferably for oral use, they may also be formulated for and administered by other methods which are known for administering analgesics, e.g. suppositories. Also, the preferred dosage levels mentioned earlier are used in adults; paediatric compositions would contain proportionally less of the active ingredients.

The compositions of the present invention can be conveniently administered by any route of administration suitable for the selected NSAID and/or selected narcotic analgesic component, e.g. oral or rectal. Preferably, the combination is formulated with any suitable nontoxic pharmaceutically acceptable inert carrier material. Such carrier materials are well known to those skilled in the art.

In a typical preparation for oral administration, e.g. tablet or capsule, the selected NSAID in an effective analgesic/anti-inflammatory amount and domperidone in an amount sufficient to hasten its onset and/or to control nausea and vomiting; or the selective NSAID in an effective analgesic/anti-inflammatory amount together with a selected narcotic analgesic in an amount sufficient to enhance the analgesic response and domperidone in an amount sufficient to hasten its onset and/or to control nausea and vomiting; are combined with any oral nontoxic pharmaceutically acceptable inert carrier such as lactose, starch (pharmaceutical grade), dicalcium phosphate, calcium sulphate, kaolin, manitol and powder sugar.

Additionally, when required, suitable binders, lubricants, disintegrating agents, colouring agents and coating agents can also be included. Typical binders include starch, gelatine, sugars such as sucrose, molasses and lactose, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, polyethylene glycol, ethylcellulose and waxes. Typical lubricants for use in the dosage forms can include, without limitation, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine and polyethylene glycol. Suitable disintegrators can include, without limitation, starch, methylcellulose, agar, bentonite, cellulose, wood products, alginic acid, guar gum, citris pulp, carboxymethylcellulose and sodium lauryl sulphate. Sweetening and flavouring agents and preservatives may be included, particularly when a liquid dosage form is formulated, e.g. syrup, suspension and elixir. When the dosage form is a capsule, it may contain, in addition to the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit.

CLAIMS

1. A method for eliciting an onset hastened analgesic and anti-inflammatory response and/or for combating nausea and vomiting in acute migraine attacks, comprising administering a pharmaceutical composition consisting of:

   (i) an amount of domperidone or its analogues sufficient to hasten the onset of the analgesic and anti-inflammatory response and to combat nausea in acute migraine, and

   (ii) an analgesically and anti-inflammatory effective amount of a NSAID comprising an acetic acid derivative or a pharmaceutically acceptable salt or an appropriate pure (-) or pure (+) isomeric form thereof from sulindac, diclofenac, fenclofenac, alclofenac, ibuprofen, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac and oxpinac.

2. A method for eliciting an onset hastened analgesic and anti-inflammatory response and/or for combating nausea and vomiting in acute migraine attacks, comprising administering a pharmaceutical composition consisting of:

   (i) an amount of domperidone or its analogues sufficient to hasten the onset of the analgesic and anti-inflammatory response and to combat nausea in acute migraine, and

   (ii) an analgesically and anti-inflammatory effective amount of a NSAID comprising an acetic acid derivative or a pharmaceutically acceptable salt or an appropriate (-) or (+) isomeric form thereof from sulindac, diclofenac, fenclofenac, alclofenac, ibuprofen, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac and oxpinac; together with an analgesically and anti-inflammatory effective amount of a narcotic analgesic, or its pharmaceutically acceptable salt or an appropriate pure (-) or (+) pure optical isomer.

3. A pharmaceutical composition of matter for use in eliciting an onset hastened analgesic and anti-inflammatory response and for combating nausea in acute migraine attacks, comprising administering a pharmaceutical composition consisting of:

   (i) an amount of domperidone or its analogues sufficient to hasten the onset of the analgesic and anti-inflammatory response and to combat nausea in acute migraine, and

   (ii) an analgesically and anti-inflammatory effective amount of a NSAID comprising an acetic acid derivative or a pharmaceutically acceptable salt or an appropriate (-) or (+) isomeric form thereof from sulindac, diclofenac, fenclofenac, alclofenac, ibuprofen, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac and oxpinac.

4. A pharmaceutical composition of matter for use in eliciting an onset hastened analgesic and anti-inflammatory response and for combating nausea in acute migraine attacks, comprising administering a pharmaceutical composition consisting of:

   (i) an amount of domperidone or its analogues sufficient to hasten the onset of the analgesic and anti-inflammatory response and to combat nausea in acute migraine, and

   [redacted] isomeric form thereof from sulindac, diclofenac, fenclofenac, alclofenac, ibuprofen, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac and oxpinac; together with an analgesically and anti-inflammatory effective amount of a narcotic analgesic, or its pharmaceutically acceptable salt or an appropriate pure (-) or pure (+)isomer.

5. A pharmaceutical composition according to claims 3&4, wherein the NSAID is a propionic acid derivative.

6. A pharmaceutical composition according to claims 3&4, wherein the NSAID is a fenamic acid derivative.

7. A pharmaceutical composition according to claims 3&4, wherein the NSAID is a biphenylcarboxylic acid derivative.

8. A pharmaceutical composition according to claims 3&4, wherein the NSAID is an oxicam derivative.

9. A pharmaceutical composition according to claims 3&4, said composition being adapted for oral administration.

10. A pharmaceutical composition according to claims 3&4, said composition being formulated as a tablet or capsule.

11. A pharmaceutical composition according to claim 10, wherein said composition is being formulated as a dispersible or effervescent dosage form.

12. A pharmaceutical composition according to claim 10, wherein said composition is in enteric coated dosage form.

13. A pharmaceutical composition according to claim 10, wherein said composition is in sustained or modified or time release form.

14. A pharmaceutical composition according to claim 10, wherein said composition is in microencapsulated dosage form.

15. A pharmaceutical composition according to claims 3&4, said composition being formulated as granules for oral administration.

16. A pharmaceutical composition according to claims 3&4, said composition being adapted for rectal administration.

17. A pharmaceutical composition according to claim 17, said composition being formulated as a suppository.

18. A pharmaceutical composition according to claim 17, said composition being formulated as an enema or rectal solution.

The Patent Office

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Application No: GB 9613410.1 **Examiner:** Mr S.J.Pilling
Claims searched: 1 to 18 **Date of search:** 10 October 1996

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

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Int Cl (Ed.6): A61K 31/445

Other: ONLINE: CAS ONLINE, WPI, JAPIO, CLAIMS, DIALOG/MEDICINE

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X	EP 0327040 A2 (SIKIRIC *ET AL*) 09.08.89 (see also WPI Abstract Accession No. 89-229090/32)	1-4
X	Therapia. Hungarica. Vol. 38. No. 4. 1990. (Hungary) Z Zahumenszky & E Farkas. "*The role of a peripheral dopamine-antagonist (Motilium) in improving the tolerance to steroidal and non-steroidal anti-inflammatory agents*". pages 156 to 159.	1-6,8-10
X	Postgrad. Med. J. Suppl., Vol. 55. No. 1. 1979. L Depuydt *et al*. "*The effect of domperidone on the gastric tolerance and the efficacy of non-steroidal anti-inflammatory drugs on osteo-arthritis*". 52	1-4,9,10

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.